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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/770,639	02/02/2004	Francisco Sanchez-Madrid	27331-501CIP2A	1583

30623 7590 12/01/2009
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EXAMINER

SKELDING, ZACHARY S

ART UNIT	PAPER NUMBER
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1644

MAIL DATE	DELIVERY MODE
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12/01/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/770,639	Applicant(s) SANCHEZ-MADRID ET AL.	
	Examiner ZACHARY SKELDING	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 November 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 56,59,60 and 105-115 is/are pending in the application.
- 4a) Of the above claim(s) 109-115 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 56,59,60 and 105-108 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. In view of the panel decision regarding the Pre-Appeal Brief filed November 6, 2009, PROSECUTION IS HEREBY REOPENED. New Grounds of Rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

2. Disposition of the claims:

Claims 56, 59, 60 and 105-115 are pending.

Claims 56, 59, 60 and 105-108 are under examination wherein the elected species of unwanted immune response to be treated is "rheumatoid arthritis".

Claims 109-115 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species of invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 6, 2006.

This Office Action is in response to applicant's pre-appeal brief filed November 6, 2009.

The previous rejections under 35 U.S.C. § 103(a) has been withdrawn upon reconsideration.

A New Grounds of Rejection is put forth below.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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4. Claims 56, 59, 60 and 105-108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Choy et al. (British Journal of Rheumatology 1998;37:484-490, cited herewith), Marzio et al. (Immunopharmacol Immunotoxicol. 1999 Aug;21(3):565-82), Black et al. (Arthritis Res. 2002;4(3):177-83, cited herewith), McInnes et al. (Nat Med. 1997 Feb;3(2):189-95, hereafter "McInnes 1997"), McInnes et al. (Immunol Today. 1998 Feb;19(2):75-9, hereafter "McInnes 1998"), Strom et al. (US 2002/0114781, cited herewith) and Christine White (US 20020039557).

Choy teaches that while anti-lymphocyte antibodies were shown to produce long-lasting disease suppression in animal models of rheumatoid arthritis, clinical trials using anti-lymphocyte antibodies, such as depleting anti-CD4 antibodies, in human rheumatoid arthritis patients failed for a variety of reasons (see Choy Abstract and page 487, right col., 2nd paragraph).

In particular, Choy teaches how the previous failures of depleting anti-lymphocyte antibodies in human rheumatoid arthritis clinical trials may be attributed to three major factors:

“First, some of the T cells targeted are not the pathogenic T cells in RA.

Second, severe and prolonged lymphopenia after treatment increases the risk of long term immunosuppression and precludes the use of high doses of mAbs.

Third, depleting antibodies are more efficient in eliminating naive, circulating T cells than the activated, pathogenic T cells present in the joint.”

(see *ibid*).

Choy further teaches the following (emphasis added):

“The fact that depleting antibodies are more efficient in eliminating naive and circulating T cells than the activated, memory pathogenic T cells resident in the joint, was illustrated by experience with both Campath-1H and cM-T412 antibodies. Campath-1H is a humanized anti-CDw52 mAb. The CDw52 molecule is present on the surface of T cells, monocytes and B cells. Campath-1H is extremely potent in inducing complement-mediated lysis. In open studies, tender and swollen joint scores reduced by 50% without significant changes in ESR or CRP [37, 38]. Campath-1H induced a profound and protracted lymphopenia after treatment. In the high-dose groups, there was prolonged absence of circulating lymphocytes. Nevertheless, disease improvement did not correlate with lymphopenia such that disease relapse occurred in the presence of severe lymphopenia. Synovial biopsies in lymphopenic patients who relapsed showed that there were diffuse mononuclear infiltrates with CD4+ and CD8+ lymphocytes still present [39] so that the changes in peripheral blood were not reflected in the synovium.

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The experience with the chimeric depleting anti-CD4 mAb, cM-T412 (Centocor Inc.), further highlights this problem. cM-T412 produced a dose-dependent reduction in the number of circulating CD4⁺ lymphocytes which was protracted when high doses were given, especially with concomitant methotrexate [40, 41]. ***Clinical improvement was variable and correlated with synovial fluid, but not peripheral blood changes.*** After a single 50 mg dose of cM-T412, there was a severe CD4 lymphopenia and >90% of the peripheral blood CD4⁺ lymphocytes were coated with cM-T412. ***In contrast, there was no change in synovial fluid CD4⁺ lymphocyte number and only 11% of synovial CD4⁺ cells were coated with cM-T412.*** After five daily treatments with cM-T412, there was a statistically significant reduction in the number of synovial fluid CD4⁺ lymphocytes. Interestingly, the percentage of synovial fluid lymphocytes coated with cM-T412 varied greatly among patients; crucially, the percentage of cM-T412-coated synovial lymphocytes correlated with the percentage of clinical improvement [41].

These results suggested that, when cM-T412 is given i.v., it binds to peripheral blood CD4 targets. Most of these cells do not contribute significantly to synovitis. One may construe that the dose and treatment regimen of cM-T412 are critical in producing a clinical response because these determine the amount of cM-T412 entering the joint. Among the synovial CD4⁺ lymphocytes, most are recruited non-specifically to the joint and only a small proportion are the disease-driving arthritogenic lymphocytes. ***Therefore, if one aims to improve arthritis by depleting synovial CD4⁺ lymphocytes, sufficiently high doses must be given to achieve significant concentration in the joint. However, at these doses of depleting mAbs, there may be severe depletion of peripheral CD4⁺ lymphocytes for a prolonged period, resulting in an unacceptable level of immunosuppression. This principle is likely to apply to all depleting anti-T-cell mAbs.*** Therefore, the T-cell-depletion strategy has been abandoned in favour of a strategy aiming to tolerize T cells.”

Choy differs from the claimed invention in that it does not teach the use of depleting anti-CD69 antibodies to treat rheumatoid arthritis.

However, Marzio teaches although CD69 is absent on peripheral blood resting lymphocytes, e.g., naive T cells, "CD69⁺ T cells have been detected at remarkably high levels in synovial fluid and synovial membrane from chronic rheumatoid arthritis patients and, to a lesser extent, in patients suffering from other types of chronic synovitis." (see Marzio paragraph bridging pages 572-73).

Furthermore, in this regard one of ordinary skill in the art knows that not only do peripheral blood *resting* lymphocytes *not* express CD69 as taught by Marzio, but also peripheral blood

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memory T-cells (CD45RO+) and activated T cells (HLA-DR+) *also do not* express CD69 as shown in Figures 1 and 2 of Black (see especially part (a) of each).

Thus, one of ordinary skill in the art would have known that the overwhelming majority of peripheral blood T-lymphocytes do not express CD69.

In contrast, the T cell surface protein CD69 is found at remarkably high levels on T cells in the synovial space of rheumatoid arthritis patients.

Therefore, CD69+ T cells are exceptionally selectively localized to the site where rheumatoid arthritis pathogenesis occurs.

Moreover, McInnes 1997 teaches the CD69+ T cells found in the rheumatoid synovium are responsible for activating TNF α release from macrophage/monocytes via a mechanism dependent on cell-cell contact. (see page 193, right column, last paragraph; page 189-90 bridging paragraph; column bridging paragraph page 192; and Figure 6). Importantly, McInnes 1997 discloses the CD69+ T cell induction of TNF α production by macrophage/monocytes was “***almost completely abrogated by addition of anti-CD69 antibody.***” (see McInnes #1 page 192, right column, 1st paragraph and Figure 7).

This teaching of McInnes 1997 would be instantly recognized by one of ordinary skill in the art as being of substantial importance given the well known ability of TNF α inhibitors to treat rheumatoid arthritis (see McInnes 1997 at page 189, right column, 1st paragraph).

McInnes 1998 is a review article that summarizes the findings of McInnes 1997 concerning the role of IL-15 induction of CD69 on CD45RO+ T cells, and in turn the role of these CD69 expressing T cells in inducing TNF α production by synovial macrophage. (see McInnes 1998 at page 76, right column 1st paragraph and Box 1; the paragraph bridging pages 76-77 and Figure 1).

With regard to clinical strategies for the treatment of rheumatoid arthritis, McInnes 1998 teaches in the paragraph bridging pages 77-78 that "cell-directed therapies that not only inhibit T-cell activation but also deplete T cells from the synovial compartment, or at least interfere with their membrane interactions, will probably be most efficacious. It is of interest that clinical improvement following anti-CD4 therapy in RA correlates with synovial T-cell coating with anti-CD4.”

Given the reference teachings it would have been obvious to one of ordinary skill in the art that depleting anti-CD69 antibodies would be reasonably predicted to successfully address the short-comings of previous attempts to treat human rheumatoid arthritis patients with depleting anti-lymphocyte antibodies described by Choy, thereby providing one of ordinary skill in the art with a viable method for treating rheumatoid arthritis via T-lymphocyte depletion.

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More specifically, one of ordinary skill in the art would immediately recognize that unlike a depleting anti-CD4 or anti-CDw52 antibody whose activity is instantly diluted by binding to all of the peripheral blood CD4+ T cells which do *not* contribute to disease pathogenesis (see, e.g., Choy at page 488, left col., 1st paragraph through col. bridging paragraph), ***a depleting anti-CD69 would be exceptionally specific for the T cells found at the site of rheumatoid arthritis pathogenesis.*** For this reason one of ordinary skill in the art would have a reasonable expectation of being able to administer a depleting anti-CD69 antibody at a dose that could effectively deplete the T-cell found in the synovial joint of a rheumatoid arthritis patient.

One of ordinary skill in the art would have had a reasonable expectation of successfully using a depleting anti-CD69 antibody to treat rheumatoid arthritis given the remarkably high levels of CD69+ T cells in the rheumatoid synovium and the absence of naïve, memory and activated CD69+ T cells in the peripheral blood, and further given the showing of McInnes #1 that the memory T cell induction of TNF α production by macrophage/monocytes is “almost completely abrogated by addition of anti-CD69 antibody.”

Moreover, one of ordinary skill in the art would have been motivated to make use of a depleting anti-CD69 antibody to treat rheumatoid arthritis given the teachings of McInnes #2 that “cell-directed therapies that not only inhibit T-cell activation but also deplete T cells from the synovial compartment, or at least interfere with their membrane interactions, will probably be most efficacious.” Of course, as would be obvious to one of ordinary skill in the art, the best possible anti-CD69 agent would be one that both inhibits the interaction of CD69 expressing T cells with synovial macrophage thereby inhibiting TNF α production and at the same time triggers the depletion of CD69 expressing T cells.

As to making a depleting anti-CD69 to be used in the claimed method, it was well within the knowledge of one of ordinary skill in the art that antibodies binding to a cell surface protein can be made to be depleting in vivo by ensuring that said antibody has the appropriate Fc region for antibody dependent cell cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC) (see Strom, e.g., at page 6, paragraphs [0052-0055] and page 7, paragraph [0064-0068]). Thus, one of ordinary skill in the art would know how to make a depleting anti-CD69 antibody that could be used to treat rheumatoid arthritis.

It further would have been equally obvious to one of ordinary skill in the art that an anti-CD69 antibody can also be made depleting by conjugating said antibody to a second therapeutic agent, such as a radioisotope, which will damage the cells to which it binds (see, e.g., Christine White which describes the preparation of naturally depleting or conjugated anti-lymphocyte antibodies to treat rheumatoid arthritis, see claim 3; page 3, paragraph [0026]; page 7, paragraph [0075]; and page 19, paragraphs [0217-219]).

Of course, an antibody conjugated to a radioisotope AND having an Fc region capable of mediating ADCC and/or CDC would be reasonably expected by one of ordinary skill in the art to be the most depleting of all.

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Thus, it would have been obvious to one of ordinary skill in the art, and one of ordinary skill in the art would have been able to prepare a depleting anti-CD69 antibody that depletes cells either via conjugation of said antibody to a second therapeutic agent and/or by ensuring that said antibody has the appropriate Fc so as to mediate ADCC and/or CDC.

Thus, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Thus, the instant claims are unpatentable over Choy in view of Marzio, Black, McInnes 1997, McInnes 1998, Strom and White.

Response to applicant's arguments

Applicant's arguments put forth in the Pre-Appeal Brief filed November 6, 2009, in so far as they are germane to the rejection put forth above, are addressed further below.

Applicant argues:

1. the references teachings allegedly fail to provide an enabling disclosure for "the *in vivo* use of any depleting anti-CD69 antibody molecule for the treatment of rheumatoid arthritis";
2. one of ordinary skill in the art would not have been motivated to substitute a depleting anti-CD69 antibody for the depleting anti-CD4 antibody of Van der Lubbe et al. (J Autoimmun. 1997 Feb;10(1):87-97) in the treatment of rheumatoid arthritis because the references allegedly would not have provided one of ordinary skill in the art with a reasonable expectation of successfully making such a substitution;
3. when considered as a whole the McInnes 1998 reference allegedly teaches away from the claimed invention; and
4. because the instant specification teaches use of a *non-depleting* anti-CD69 antibody was not effective in the murine collagen-induced arthritis model.

Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed July 17, 2009 and for the reasons put forth below.

As to (1), as stated in the New Grounds of Rejection put forth above, it was well within the knowledge of one of ordinary skill in the art that antibodies binding to a cell surface protein can be made to be depleting *in vivo* by ensuring that said antibody has the appropriate Fc

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region for ADCC or CDC. Thus, one of ordinary skill in the art would know how to make a depleting anti-CD69 antibody that could be used to treat rheumatoid arthritis.

As to (2), applicant's argument is also not found convincing.

First, applicant's argument does not adequately address why, even if, *arguendo*, a depleting anti-CD69 antibody were to be less efficient at depleting memory T cells one of ordinary skill in the art would lack a reasonable expectation of successfully using an anti-CD69 antibody to treat rheumatoid arthritis *in light of the exceptional specificity that a depleting anti-CD69 antibody would be expected to have for the T cells found at the site of rheumatoid arthritis pathogenesis (see the New Grounds of Rejection put forth above).*

Secondly, applicant has not provided sound scientific reasoning or objective evidence to support their assertion that one of ordinary skill in the art would assume a depleting anti-CD69 antibody would have properties similar to a depleting anti-CD4 antibody with respect to depletion of memory T cells.

In contrast, based on the teachings of the prior art one of ordinary skill in the art would have a reasonable basis to believe that a depleting anti-CD69 antibody would *not* behave the same as a depleting anti-CD4 antibody in this regard.

In particular, Van der Lubbe suggests that at least one mechanism by which anti-CD4 antibody may preferentially deplete naive T cells over CD45RO+ memory T cells is by a T-cell receptor (TCR) signal counteracting anti-CD4 antibody induced cell death (see Van der Lubbe at page 95, right col., 1st paragraph, referencing Chace et al., J. Immunol. 1994;152:405-412, cited herewith). The Chace reference cited by Van der Lubbe describes this mechanism in greater detail at page 411, left col., 2nd paragraph where it is made clear that the close physical and function association of CD4 with the TCR is important for this TCR rescue of anti-CD4 induced cell death. In contrast, there is no a priori reason for one of ordinary skill in the art to assume that the T-cell killing effect of a depleting anti-CD69 would be similarly effected by TCR signaling because there is no a prior reason to believe these molecules are similarly physically and functionally associated.

Another mechanism by which CD4+ memory T-cells resist anti-CD4 depletion suggested by Van der Lubbe is that they may resist apoptosis due to their association with stromal cells (see Van der Lubbe at page 95, right col., 1st paragraph). However, the significance of such a mechanism to an anti-CD69 antibody that acts via ADCC and/or CDC and/or via radioisotope conjugation to deplete T cells (none of which primarily depend on apoptosis for cell killing) would be unclear to one of ordinary skill in the art.

As to (3), applicant's argument is not found convincing because when applicant argues that the statement from the McInnes 1998 review that "T-cell-directed therapies that not only inhibit T-cell activation but also deplete T cells from the synovial compartment, or at least interfere with their membrane interactions, will probably be most efficacious," would be

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interpreted by one of ordinary skill in the art as only “referring to IL-15 and/or CD4 as the targets for therapy, thereby teaching away from CD69” applicant is not sufficiently accounting for the ordinary creativity of one of ordinary skill in the art.

It is the examiner’s position that one of ordinary skill in the art having no more than ordinary creativity would as a general principal want any anti-lymphocyte antibody to be used for the treatment of rheumatoid arthritis, whether it be anti-CD69, anti-CD4 or something else, to inhibit the inflammatory activity of the disease causing cells in the rheumatoid joint by as many mechanisms as possible, for example, by depleting T cells from the synovial compartment, AND by inhibiting T-cell activation in the synovial compartment, AND by interfering with T-cell-membrane interactions in the synovial compartment. The teachings of McInnes 1998 merely provide explicit support from the art for this general principal.

Consistent with the reasoning given above, it is worth noting that obviousness is viewed through the lens of a person of ordinary skill in the art with consideration of common knowledge and common sense. *Dystar Textilfarben GMBH & Co. Deutschland KG v. C.H.Patrick Co.*, 464 F.3d 1356, 1367, 80 USPQ2d 1641, 1650 (Fed. Cir. 2006).

Furthermore, as stated in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1742, 82 USPQ2d 1385, 1397 (2007), “[a] person of ordinary skill is also a person of ordinary creativity, not an automaton,” and “[a] court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” *Id.*

As to (4), applicant's argument is not found convincing essentially for the reasons of record put forth in the final Office Action mailed July 17, 2009 and because it is unclear what applicant is arguing – the instant claims and the instant rejection are directed to using a depleting anti-CD69 antibody to treat rheumatoid arthritis. In contrast, applicant is asserting “even assuming, *arguendo*, that a person of ordinary skill in the art would have been motivated to use the *non-depleting, neutralizing* CD69 antibody used in McInnes 1997 for the treatment of RA, the person of ordinary skill in the art would have been unsuccessful and would not have arrived at the present invention.” It is unclear to the examiner how using a *non-depleting, neutralizing* anti-CD69 antibody relates to the claimed invention.

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

5. No claim is allowed.
6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Zachary Skelding/
Examiner, Art Unit 1644